This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

UPDATE NOTICE

Please note that the *Guidance for Preparation of PMA Manufacturing Information (March 22, 1991)* in pages iv-79 through iv-87 in the Premarket Approval Manual was updated on August 1992. This updated guidance document is included as an insert. It is also available as a separate shelf item (shelf number #448) from DSMA by calling 1-800-638-2041 or on the Facts-on-Demand (#448) by dialing 1-800-899-0381 .

GUIDANCE FOR PREPARATION OF PMA MANUFACTURING INFORMATION

Purpose

This guidance has been prepared by the Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), and the Office of Compliance and Surveillance (OCS) to assist device manufacturers in preparing and maintaining manufacturing information required in premarket approval applications (PMA) and PMA supplements.

Device manufacturers include not only facilities that manufacture or assemble the finished device but also facilities operated or contracted by the PMA applicant to perform a segment of the manufacturing operation such as sterilization or packaging. Contracted facilities may either provide the required manufacturing information applicable to their operation directly to the PMA applicant for inclusion in the PMA submission, or submit such information directly to CDRH in a Device Master File. The PMA applicant should provide written authorization to reference the Device Master File information in the PMA submission.

This guidance, when used by the PMA applicant, in conjunction with the requirements under 21 CFR Part 820 (Good Manufacturing Practice for Medical Devices: General), is intended to ensure that the manufacturing section in the PMA complies with the content requirements under 21 CFR 814.20(b)(4) and is sufficiently complete and appropriately organized to permit FDA to initiate and complete a good manufacturing practice (GMP) inspection of the manufacturing facility(s) before and after CDRH approval of the PMA submission.

PMA Manufacturing Section Review Process

With the implementation of Compliance Program 7383.001 (Medical Device Premarket Approval and Postmarket Inspections) in January 1991, significant changes in the review of the PMA manufacturing information occurred. PMA inspections conducted since 1978 were usually limited to both assessing the firm's capability to manufacture the device as claimed in the PMA and confirming that the firm's quality assurance system was in compliance with the requirements of the GMP regulation (21 CFR Part 820). The above Compliance Program directs FDA field offices to consider the extent to which the firm has established a formal quality assurance program and has assured that the approved design is properly translated into specifications via process validation.

Simultaneous with the ODE review of an original PMA or a PMA supplement requesting approval for an alternate or additional manufacturing facility, OCS will review the manufacturing information in the PMA submission. In making the determination of the firm's ability to manufacture or process the device which is the subject of the PMA submission, OCS may issue an inspection assignment to the appropriate FDA district office. The inspection

assignment will be issued when ODE has filed the submission and OCS has determined that the manufacturer has demonstrated in the PMA submission that the manufacturing process has been documented. All assignments will be accompanied by a copy of the manufacturing section, draft labeling, and the description of appropriate device characteristics included in the PMA submission. Under certain conditions, OCS and the district office may decide that an inspection is not necessary.

If the applicant is informed that a reinspection is necessary before approval of the PMA submission, all questions regarding the reinspection should be directed to the appropriate FDA District Office in the case of a domestic facility or to the following FDA office in the case of a foreign facility:

Food and Drug Administration
Office of Regional Operations
International Programs
and Technical Support Branch (HFC-133)
5600 Fishers Lane
Rockville, Maryland 20857
(301) 443-1855

In those cases where an inspection is not assigned, the district office may be requested to either concur in approval or to report information which may warrant delay of approval.

Compliance Program 7383.001 also provides for a post-approval inspection to be conducted within 8 months of CDRH approval of the PMA submission. This inspection will primarily focus on any changes that may have been made in the device design, manufacturing process, or quality assurance systems. Prior to this post-approval inspection, the district office will be provided with the PMA holder's final printed labeling and any relevant information regarding approved and pending PMA supplements submitted in the interim.

Suggestions

1. In the cover letter for the PMA or PMA supplement:

   - Provide the full name, address (street address rather than P.O. Box), telephone number (including area code), and FDA establishment registration number (if available) for each facility to be used in the assembly, sterilization, or packaging of the device.

   - Indicate whether each facility is presently prepared to be inspected and, if not, when it will be prepared.

- Identify any facility that has been previously inspected by FDA relative to its manufacture or processing of a similar device and provide the dates of the most recent FDA inspection. Such facilities may not require reinspection prior to approval of the PMA submission.

- Acknowledge when the PMA submission lacks complete manufacturing information, request (with appropriate justification or explanation) a waiver to delay the submission of this information, and provide a reasonable date when the PMA submission will be amended to include such. This amendment may be considered a major amendment that restarts the 180-day review period for the PMA submission.

- If required manufacturing information is to be included in the PMA submission by authorized reference to a Device Master File, indicate such in the cover letter and include an original of the Device Master File holder's written authorization.

2. The manufacturing section for each copy of a PMA submission should be submitted in a separate volume or volumes of no greater than 2 inches thickness each.

   However, when multiple facilities are involved in the assembly or processing of the device, applicable manufacturing information for each facility should be submitted in a separate volume or volumes identified as to the facility to which it applies. The initial volume for each facility should include the following:

   - A copy of the PMA cover letter with the information in Item 1;

   - A table of contents;

   - A complete description of the device including pictorial representations;

   - A complete description of each of the functional components or ingredients of the device if the device consists of more than one physical component or ingredient;

   - A complete description of the properties of the device relevant to the diagnosis, treatment, prevention, cure or mitigation of a disease or condition;

   - A complete description of the principle(s) of operation of the device;

   - A complete description of the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, storage and, where appropriate,

installation of the device in sufficient detail so that a person generally familiar with current good manufacturing practice (refer to 21 CFR Part 820) can make a knowledgeable judgment about the quality systems used in the manufacture of the device. Please note that this section must now include process validation to support the proposed manufacturing method and controls. Guidance is provided under the "Format and Content of the PMA Manufacturing Section" discussion that follows; and

- o Copies of all proposed labeling for the device to include, for example, instructions for installation and any information, literature, or advertising that constitutes labeling under section 201(m) of the Food, Drug, and Cosmetic Act.

3. Each volume and each page within a volume should be numbered. Tabbed dividers between subsections will facilitate FDA review.

4. Although a PMA submission may reference manufacturing information in another of the applicant's PMA submissions, this may cause delays in OCS review of the manufacturing section for a pending PMA submission and issuance of the inspection assignment to the FDA District Office. Delays may result because of difficulties experienced by ODE in locating the referenced information and assuring that it is current; that is, it has not been superseded by manufacturing information in subsequent submissions (i.e., amendments, supplements, or periodic reports) to the applicant's PMA. Document storage limitations have required that ODE periodically send its only copy of many approved PMAs and PMA supplements for storage at the Federal Records Center and other facilities. Retrieving referenced manufacturing information and assembling a complete and current manufacturing section may be a matter of several weeks to several months and in some cases may be an impossible task. To expedite OCS review of the manufacturing section and any required FDA inspection of the manufacturing site(s), the PMA applicant should resubmit, rather than reference, applicable manufacturing information already on file with FDA.

5. Although a PMA supplement for a new manufacturing/processing facility for the device must, by necessity, include a complete description of the new facility and both identify and describe all methods and controls to be employed at this facility that differ from those previously described and approved in the PMA, the PMA supplement may reference other applicable manufacturing information previously submitted in this PMA. The PMA applicant, however, should be guided by the discussion in Item #4 above as to the advisability of referencing or resubmitting this information. Resubmission is particularly advisable when the current manufacturing information is on file with ODE but is scattered throughout several submissions because of updating and other revisions.

6. Whenever previously submitted manufacturing information is resubmitted (as discussed in Items #4 and #5 above), it will not be accepted by FDA unless it is accompanied by the following statements signed by the applicants to the effect that: (1) the resubmitted information does not include a change in the device's design, specifications, composition, packaging, labeling, manufacturing/processing methods, or quality controls for which a PMA supplement is required under 21 CFR 814.39 but is not approved by or is pending before CDRH; and (2) the person understands that the submission to the government of false information is prohibited by 18 U.S.C. 1001 and 21 U.S.C. 331(g).

7. Firms that manufacture or process the device under contract to the PMA applicant often elect to submit all or a portion of the manufacturing information applicable to their facility directly to CDRH in a Device Master File rather than to the PMA applicant. This is primarily because of the trade secret or otherwise proprietary nature of some of this information. Because many such firms perform similar operations for other devices and products, information in the Device Master File may not specifically identify and describe the methods, equipment, and controls to be used in the manufacture or processing of the applicant's device. PMA applicants should inform such firms that detailed information specific to the applicant's device is required and should provide the firm with a copy of this guidance document. This guidance will assist the firm in developing or amending its Device Master File to include such information. General guidance for the preparation and submission of a Device Master File will be found on pages III-1 through III-5 of the Premarket Approval Manual available upon request from the CDRH Division of Small Manufacturers Assistance by calling 1-800-638-2041 (in Maryland, call 301-443-6597). Do not submit requests to review Drug Master Files.

FORMAT AND CONTENT OF THE PMA MANUFACTURING SECTION

Provide the following information for each device and each facility identified in the application. Address all items for each original application. Address all pertinent items for each supplement.

A. Critical/Non-Critical Device Status

1. Indicate whether the device is currently on the critical device list.

2. If the device is not currently on the critical device list, indicate and provide rationale on whether it meets the 21 CFR 820.(f) definition of a critical device.

3. For critical devices, provide a list of which components are critical and which operations are critical. Describe your rationale for their selection.

4. For critical devices, provide a list of critical operations. Indicate how critical operations will be performed and how they will be documented.

B. Organization and Personnel

1. Describe and provide appropriate documentation to demonstrate each company's quality assurance program. Include an organizational chart outlining areas of responsibility and channels for implementing corrective actions.

2. Provide a copy of each company's employee training program and examples of documentation used to assure that personnel have proper training and experience, including quality assurance personnel.

C. Quality Assurance Program

1. Describe the methods used to identify and resolve quality problems and assure that effective corrective action is implemented when needed.

2. Describe the quality data sources (i.e., complaints, service records, and inspection/test results) that are monitored to detect quality deviations.

D. Quality Audits

1. Provide a copy of the written procedures used to audit the quality assurance program of each facility.

2. The procedure should include the following:

   a) Auditor qualifications,
   b) Areas audited and criteria for auditing frequency,
   c) Reporting requirements,
   d) Distribution and who is required to review the reports, and
   e) Responsibility for follow-up and assuring effective corrective action is taken where needed.

E. Buildings and Environments

1. Describe how each facility is designed to prevent mix-ups and assure orderly handling. Provide a diagram of the physical layout of the buildings(s) and the operations within them.

2. Where environmental conditions could have an adverse effect on the device's fitness for use, provide a copy of the written procedures established to control and monitor environmental conditions (i.e., lighting, humidity, air pressure, filtration, nonviable and viable particulates, and electrostatic discharge). Include a description of the following:

   a) Environment specifications and action limits,
   b) Types and locations of controls,
   c) Documentation of inspections used to verify proper functioning of the controls,
   d) Frequency of inspections,
   e) Examples of documentation of inspections, and
   f) Procedures for corrective action.

3. Describe your rationale for any special attire used in each facility's manufacturing operations.

4. Provide a copy of appropriate procedures and schedules for the cleaning and sanitizing of all manufacturing areas. Include documented procedures for contamination control where failure to do so could adversely effect the device's fitness-for-use.

F. Equipment

1. Provide a list of all manufacturing equipment which will be maintained. Provide examples of maintenance schedules. Describe how maintenance will be documented and how the schedules will be made readily accessible.

2. Provide a copy of appropriate written procedures for the use and removal of any manufacturing material (i.e., degreasers, cleaning agents, and ethylene oxide residues). Describe how the removal will be documented.

3. Provide a list of all equipment which will need to be calibrated. Provide a copy of a general calibration procedure and/or provide calibration procedures for a few significant pieces of equipment. Provide examples of calibration records. The procedures should include provisions for accuracy and precision limits.

4. If computers are used as part of an automated production or quality assurance system, provide validation protocols for the software and, if available, the validation records and conclusions.

G. Acceptance and Control of Components

1. Provide a copy of the written procedures for general acceptance of components, and for the acceptance of several significant components. Provide examples of component acceptance/rejection records. Include receipt, inspection/sampling/testing, acceptance, storage, handling, and rejection procedures.

2. For critical devices, provide a copy of the written acceptance procedures for all critical components. Also, provide examples of records used to determine the percent of deficient critical components for each lot, the percent of lots rejected, and the quality history of a supplier. Include the statistical rationale for the sampling plan used, and include testing procedures.

3. Provide a copy of the general acceptance criteria, or a few specific acceptance criteria, for manufacturing materials, in-process materials, packaging materials, labeling, and finished devices.

4. Describe and provide a copy of the procedures for the identification of released, rejected, quarantined, or unchecked components, packaging, labeling, and incoming materials.

H. Production and Process Controls

1. Describe the manufacturing process(es) for the device, and include a flow diagram of the process(es) for each facility used.

2. Provide a copy of the written procedures for the process(es) identified in the flow diagram.

3. Provide a copy of the general validation procedure or program. Provide a list of all significant manufacturing processes (i.e., sterilization, packaging, injection molding, wave soldering, and aseptic filling) and testing procedures (i.e., bonding, welding, tensile strength, and

automated test equipment), and all critical operations and specific testing procedures, which require validation. Provide each validation protocol and, if available, the validation data and conclusions.

4. The validation program should include validation of the methods and procedures used to monitor and control the processes after validation, to assure they consistently operate within acceptable process parameters. Provide a copy of the monitoring and control procedures for each significant manufacturing process.

5. Describe reprocessing methods for devices and components. Provide a copy of the reprocessing procedures. Include reprocessing validation protocols and, if available, validation data and conclusions.

I. Document Control

1. Describe the methods and provide any procedures used to develop, maintain, and control all documentation generated to meet GMP requirements. Include:

   a) Methods used to assure all documentation is reviewed for accuracy and approved before release.
   b) Methods used to assure that only current, acceptable documentation is used.

2. Provide a copy of the formal approval procedures for device specification changes and for manufacturing process changes. Describe how the change control will be properly reviewed, how the changes are verified/validated before implementation, and how the changes are implemented in a timely manner.

J. Packaging and Labeling Control

1. Describe the label control method and the label operation itself, and indicate whether lot numbers and expiration dates are used.

2. Describe the device packaging and the shipping container. Indicate any tests performed to demonstrate that the device will be protected from alteration or damage during storage and shipping.

K. Holding, Distribution, and Installation

1. Provide a copy of the procedures for warehouse control and distribution.

2. If the device is installed, provide a copy of the procedure for its installation.

L. Device Evaluation

1. Provide a copy of the written procedures for finished device inspections and testing. If 100% inspection and testing is not performed, indicate the sampling plan utilized, and provide the statistical rationale for the plan. Describe how finished devices are quarantined prior to release.

2. Describe how critical device or component failures will be investigated. Provide a copy of the procedures and an example of a written record for investigations, to include:

   a) Criteria for initiating an investigation,
   b) Responsibilities for carrying out the investigations and assuring follow-up and corrective action,
   c) How and to whom, the investigation results are communicated, and
   d) Recordkeeping, to include investigation conclusions and follow-up.

3. Describe how failure investigations will be performed on devices which have been released and then found to have not met their performance specifications. Provide a copy of the procedures and an example of a written record for investigations, to include conclusions and follow-ups.

M. Records

1. Provide a reference list of documents which make up the device master record (DMR) for each device, at each facility.

2. In addition, include any other specific documents of the DMR, not requested in other sections of this guidance document, which will facilitate FDA's review.

3. Provide copies of records which make up the device history record (i.e., routing forms, data sheets, and batch records).

4. Provide a copy of the procedures used to establish and maintain the device master record and to control changes to the device master record.

5. Describe the complaint procedures, including the methods used to assure that all complaints received are properly reviewed, evaluated and, where necessary, investigated. Provide copies of records used in complaint processing.

6. Describe how service/repair records are maintained and reviewed.

N. Sterile Devices

1. Provide a copy of the procedures used for device release to distribution (i.e., sterility testing, parametric release, biological indicator release, and process control release).

2. Provide a copy of the testing procedures used to indicate whether the packaging materials have been challenged to assure they are microbially retentive, and that the seal(s) maintain sterility.

3. Provide a copy of pyrogenicity studies which have been conducted, if applicable. Provide a copy of the test procedure, and indicate whether each lot will be tested.

4. If ethylene oxide (EO) is used as the sterilization method, provide a copy of the sterilization procedures to include aeration time, the test method to detect EO residues, the frequency of testing, and the release criteria.

O. Devices Containing Software

1. Provide a copy of the procedures for the acceptance of software, and the specifications for the software.

2. Provide a copy of the procedures for software handling, storage, and environmental controls.

3. Provide a copy of the procedures for software change or revision control.

4. Provide a copy of the procedure used for software duplication, and the procedure used to assure that the program is accurately copied.

5. Provide a copy of the procedure used for validating revisions of the original software.

Additional Information

The following FDA prepared publications may further assist in the preparation of the PMA manufacturing section and are available upon written or telephone request from the Food and Drug Administration, Center for Devices and Radiological Health, Office of Training and Assistance, Division of Small Manufacturers Assistance (HFZ-220), 5600 Fishers Lane, Rockville, MD 20857 (Phone: 1-800-638-2041 outside Maryland and 301-443-6597 in Maryland):

1. Preproduction Quality Assurance Planning: Recommendations for Medical Device Manufacturers; September 89.

2. Guidelines on General Principles of Process Validation; May 87.

3. ODE Reviewer Guidance for Computer-Controlled Medical Devices; July 88.

4. Federal Register of July 21, 1978; Good Manufacturing Practice for Medical Devices (21 CFR Part 820)

5. Federal Register of March 17, 1988; Advisory List of Critical Devices - 1988

6. Proposed Changes to the Medical Devices Current Good Manufacturing Practice (CGMP) Regulations; Information and Comment; FR Notice of Availability, November 90.

7. Application of the Medical Device GMPs to Computerized Devices and Manufacturing Processes - Medical Device GMP Guidance to FDA Investigators; Draft Guidance, November 90.